PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 504508055WO0	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/025401	International filing date *(day/month/year)* 06 August 2004 (06.08.2004)	Priority date *(day/month/year)* 07 August 2003 (07.08.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant AVI BIOPHARMA, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 13 February 2006 (13.02.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Beate Giffo-Schmitt Telephone No. +41 22 338 87 20

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	27 APR 2005
Applicant's or agent's file reference 504508055WO0	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/25401	06 August 2004 (06.08.2004)	07 August 2003 (07.08.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C12Q 1/00; A01N 57/00; A61K 31/685 and US Cl.: 435/5; 514/81, 90; 544/1

Applicant

AVI BIOPHARMA, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Janet L. Epps-Ford, Ph.D. Telephone No. 571-272-0547

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/25401

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☒ table(s) related to the sequence listing

   b. format of material

      ☒ in written format

      ☒ in computer readable form

   c. time of filing/furnishing

      ☒ contained in international application as filed.

      ☒ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/25401

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 7-13, 21-26	YES
	Claims 1-6, 14-20, 27-29	NO
Inventive step (IS)	Claims 7-13, 21-26	YES
	Claims 1-6, 14-20, 27-29	NO
Industrial applicability (IA)	Claims 1-29	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/25401

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 1 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: Claim 1, line 3, recites the phrase "selected from from," the word "from" is improperly duplicated in this claim.

WRITTEN OPINION OF THE
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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

WRITTEN OPINION OF THE
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International application No.
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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-6, 14-20, and 27-29 lack an inventive step under PCT Article 33(3) as being obvious over Stein et al. in view of Banerjee et al. and Anderson et al.

The instant claims are drawn to an oligonucleotide analog compound for use in inhibiting replication in mammalian host cells of an RNA virus having a single-stranded, positive-sense RNA genome and selected from Flaviviridae, picornoviridae. Caliciviridae, togaviridae or the coronaviridae family and hepatitis E virus, and characterized by: (1) a nuclease resistant backbone, (2) capable of uptake by mammalian host cells, (3) containing between 12-40 nucleotide bases, (4) having a targeting sequence of at least 12 subunits that are complementary to a region associated with stem-loop secondary structure within the 3-terminal end 40 bases of the negative sense RNA strand of the virus, and capable of forming a heteroduplex structure with the negative strand viral ssRNA genome having a Tm of at least 45°C.

Stein et al. provides antiviral compounds directed against an RNA virus from the picornavirus, calicivirus, togavirus or flavivirus families having a single-stranded, positive sense genome of less than 12 kb and a first open reading frame that encodes a polyprotein containing multiple functional proteins. The antiviral compound comprises a substantially uncharged oligomer having (a) a sequence of 12 to 40 subunits, supporting a targeting base sequence that is substantially complementary to a viral target sequence which spans the translation initiation region of said first open reading frame, and (b) a substantially uncharged backbone. In a preferred embodiment, the oligomer is a morpholino oligomer, having a sequence or morpholino subunits. The subunits are generally connected by uncharged, phosphorus-containing intersubunit linkages, which joining the morpholino nitrogen of one subunit to the 5' exocyclic carbon of an adjacent subunit. In one embodiment, these linkages are phosphorodiamidate linkages. The substantially uncharged oligomer will typically have a T_m, with respect to binding to the viral target sequence, of greater than about 45°C, as well as an ability to be actively taken up by mammalian cells. In addition, the compound can generally be recovered, in a heteroduplex form consisting of the oligomer and a complementary portion of the viral genome of the RNA virus, from the serum or urine of a mammalian subject, several hours after being administered to the subject. Moreover, in one embodiment of Stein et al., the antiviral compounds are directed against specific viruses or families, in particular selected embodiments include antiviral compounds directed against a picornavirus.

However, Stein et al. does not specifically teach the design of oligonucleotide analogs targeting the 3'-terminal end 40 bases of the negative-sense RNA strand of the target virus.
Banerjee et al. teach that disrupting the formation of "stem b", which corresponds to the 3'-terminal sequence of poliovirus negative strand RNA, results in the interference of 2C polypeptide binding to this region and loss of infectivity of poliovirus RNA. The 2C protein is required for initiation of viral replication (see pages 41-42 of Banerjee et al.).

Anderson et al. teach the design of oligonucleotides that have a sequence complementary to sequences associated with HBV RNA replication. This reference provides clear guidance for designing antisense compounds targeting regions of viral RNA that are required for viral replication.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention, to modify the teachings of Stein et al. with Banerjee et al. and Anderson to make the instant invention. One of ordinary skill in the art would have been motivated to modify the compositions and methods of Stein et al. to make antiviral compounds targeting the 3'-terminal region of a poliovirus (which is a member of the picornavirus family), since the prior art clearly discloses that this region is particularly needed for viral RNA replication. Moreover, the prior art provides a high expectation of success that antisense compounds targeting viral RNA sequences used for replication, would be effective to inhibit viral replication.

Claims 1-29 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.